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Brief Clinical Report

The Wolf-Hirschhorn Syndrome in Adulthood: Evaluation of a 24-Year-Old Man With a rec(4) Chromosome

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We describe a profoundly intellectually disabled 24-year-old man with Wolf-Hirschhorn syndrome, left hemiplegia, epilepsy, atrophy of the right cerebral hemisphere, and dilatation of the right ventricle. The patient had a small ventricular septal defect, was wheelchair bound, and totally dependent. He had no speech, but vocalised to show his feelings. In this patient, the del(4)(p15) was subtle and arose due to the inheritance of a recombinant chromosome (4) from a maternal pericentric inversion—46,XX,inv(4)(p15.32q35). Fluorescence in situ hybridisation with probe D4S96 confirmed the deletion. This is the second case of Wolf-Hirschhorn syndrome resulting from a large pericentric inversion of chromosome 4.

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KEY WORDS: profound mental retardation, hemiplegia, asymmetric cerebral atrophy, maternal pericentric inversion

INTRODUCTION

Wolf-Hirschhorn syndrome (WHS) is a clinically recognisable multiple congenital anomaly (MCA) syndrome. Phenotype based on over 120 cases [Lurie et al., 1980] includes a striking facial appearance with mild microcephaly, craniofacial asymmetry, high forehead, wide nasal bridge with prominent glabella, nasal beaking, hypertelorism, and epicanthic folds. Approximately 10% have a midline scalp defect and 50% ptosis. In addition, cleft lip and cleft palate have been reported and congenital heart malformations are noted in half of the cases [Wilson et al., 1981]. These descriptions have come from the study of young children. Several patients have lived past teenage years; however, the life expectancy is unknown and knowledge of the natural history of WHS in adults is limited due to the small number of published cases addressing long term outcome [Fujimoto and Wilson, 1990; Opitz, 1995; Wheeler et al., 1995].

The WHS is due to a deletion in the terminal band of chromosome band 4p16.3 [Estabrooks et al., 1993]. The most common cause is a *de novo* interstitial deletion, which accounts for 87% of cases. Approximately 13% of WHS patients have the unbalanced product of a parental chromosomal rearrangement [Lurie et al., 1980], usually a reciprocal translocation [Wheeler et al., 1995]. The number of translocations may be greater than 13% as submicroscopic translocations demonstrated by fluorescence *in situ* hybridisation (FISH) have been reported in cytogenetically normal parents and affected offspring [Goodship et al., 1991; Altherr et al., 1991]. To our knowledge, WHS due to an unbalanced pericentric inversion with a recombinant chromosome 4 has been reported only once [Hirsch and Baldinger, 1993]. This report documents the clinical findings in a 24-year-old man with WHS to add to our knowledge about the adult phenotype. WHS was the result of an unbalanced pericentric inversion inherited from his mother.

HISTORY

The patient was the 3rd child born to healthy nonconsanguinous parents when the mother was 31 and the father was 29 years old. The two other sibs were normal and there had been four first trimester miscarriages. The pregnancy was uneventful and he was delivered at 42 weeks of gestation with a birth weight 1.87 kg and length 35.5 cm (both <3rd centile). At birth he was hypotonic and was unable to suck adequately and was spoon fed from an early age. At age 8 months he had his first grand mal seizure. An EEG showed epileptogenic activity in the right cerebral regions and

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he was commenced on anti-epileptic medication. Subsequently he had several episodes of left body convulsions. At age 3 years and 4 months he was admitted for investigation of recurrent vomiting. As part of the investigation a pneumoencephalogram was performed which showed a cavum septum pellucidum. Seizure activity diminished from age 12 years and he has been seizure free from age 16 years. Developmental assessment at 2 years of age showed an overall functional level of 3–4 months. At 3 years he smiled responsively to sound but did not follow with his eyes. He had attained head control, moved his limbs restlessly (the right more than the left), and was able to roll from supine to prone. From 4 years he was cared for by a local hostel for the intellectually handicapped. The diagnosis of Smith-Lemli-Opitz syndrome had been made at 6 months of age on the basis of his appearance.

At 24 years, his height was 135 cm (≪3rd centile), weight 23 kg and he was microcephalic with head circumference 46 cm (≪3rd centile). Total hand length was 12.5 cm, palm length 7 cm, and foot length 14 cm (all below 3rd centile). A left hemiplegia was present, but tone was increased bilaterally and Babinski reflexes present. His facial appearance was consistent with adult WHS [Wheeler et al., 1995] with a high forehead, hypoplastic orbital ridges with shallow orbits, antimongoloid slant of palpebral fissures, a high nasal bridge, and prominent thin ears. The ears were asymmetrial, apparently low-set, but the left larger than the right. There was also hypertelorism, a broad forehead, arched eyebrows and a prominent nose (Fig. 1). There was a severe thoracic scoliosis to the right. He had bilateral transverse palmar creases with elongated ulnar loops on six out of ten finger tips. He had marked joint contractures of the elbows, wrists, metacarpals, hips, knees, and bilateral pes cavus with equinus foot posture due to calf contractures and toes were overlapping. Secondary sexual characteristics were underdeveloped, the left testis was in the scrotum and hypoplastic, and the right undescended. There was pubic hair but no chest hair and he was never shaved. Cardiovascular examination was abnormal with a pansystolic murmur at the left sternal edge, consistent with a small ventricular septal defect. An EEG on this occasion demonstrated left temporal epileptiform activity. The low voltage activity on the right indicated an underlying cortical abnormality. The CT scan (Fig. 2) showed a grossly atrophic right cerebral hemisphere with dilatation of the ventricle.

His overall intellectual function was approximately at an 18 month level. He was wheelchair bound, but could use a walking frame by pushing his right leg against the floor. He was totally dependent and had no speech, although he makes noises. His carers report that he indicates things he likes and dislikes and has mood swings, temper tantrums, bites his hands when excited or angry, smiles when happy, and "rocks" when sitting. He can scoop food with a spoon and can hold a special cup for drinking. He sleeps well through the night.

Cytogenetics and FISH

An initial unbanded karyotype was reported as "normal." Cytogenetic studies, repeated with high resolution banding (HRB), demonstrated a male karyotype with a deletion of 4p from p15.32 > pter (Fig. 3). All other chromosomes were normal.

The father's karyotype was normal 46,XY. The mother had a large pericentric inversion of chromosome 4;46,XX,inv(4)(p15.32q35) (Fig. 3). The patient's kary-

Fig. 1. The propositus with microcephaly, hypertelorism, arched eyebrows, and prominent nose.

Fig. 2. CT scan showing grossly atrophic right ventricle and a small ventricle on the left and microgyria.

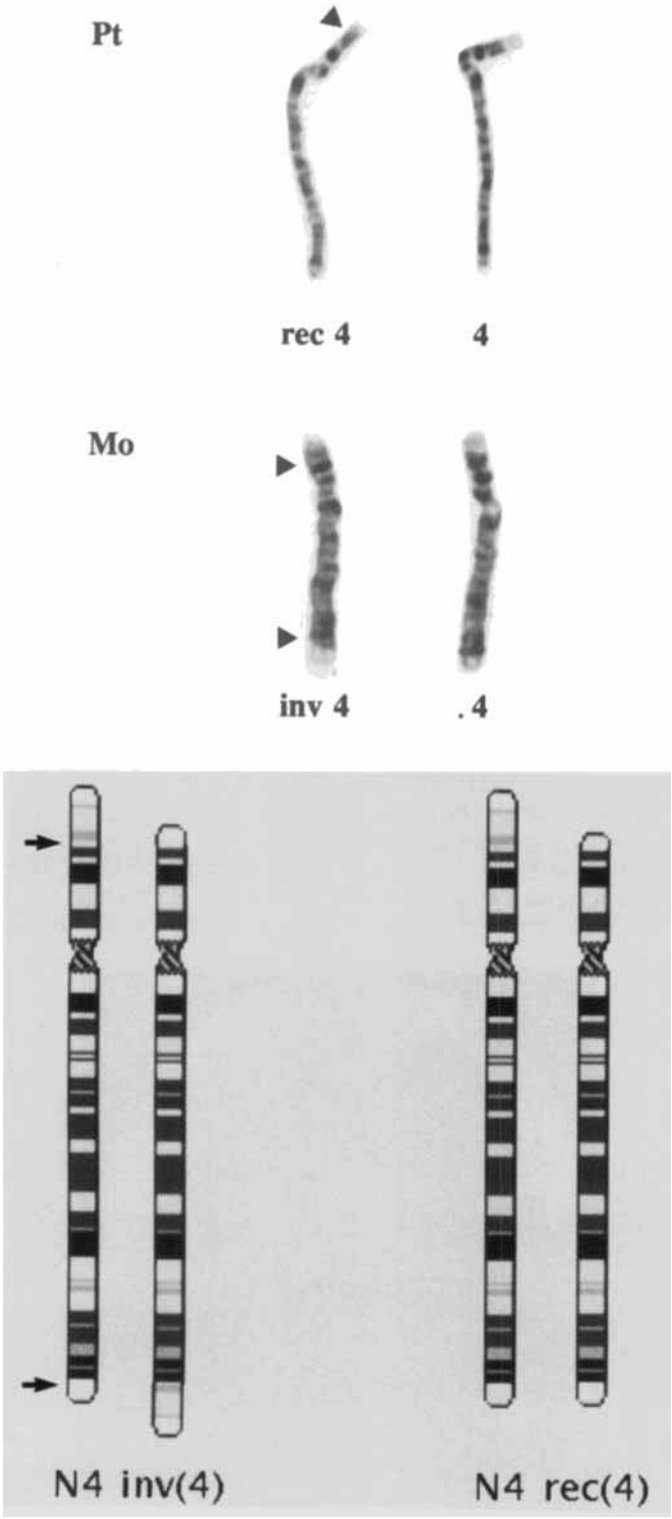

Fig. 3. Partial GTG banded karyotypes from the patient (Pt) and his mother (Mo). In each case the normal chromosome 4 is on the right. The arrows indicate the breakpoints on the short arm at p15.32 and the long arm at q35. In the patient, the chromosome material on the short arm distal to the breakpoint is the terminal segment of the long arm of chromosome 4 from q35 to the telomere. This has resulted from a crossover in the inversion loop at maternal meiosis. The patient has a duplication-deficiency recombinant chromosome 4. The ideogram shows the normal chromosome (N4), inverted 4 [inv(4)], and recombinant 4 [rec(4)] with arrows indicating the breakpoints.

otype was reassessed and in addition to the short arm deletion, duplication of the long arm from 4q35-4qter was seen distally on the short arm (Fig. 3). This chromosomal rearrangement was subtle and was not detectable on the unbanded karyotype or without HRB, as the total length of both the short and long arms of chromosome 4 were relatively unaltered. The patient's final karyotype was 46,XY,rec(4)dup q,inv(4)(p15.32q35)mat.

Probe D4S96 for the WHS region (Oncor, Gaithersburg, MD) was applied to slides (10 μl) as per manufacturer's recommendations and detection followed standard techniques [Smith et al., 1993]. A positive signal was seen on only one chromosome 4p (not shown), confirming a WHS deletion.

DISCUSSION

The detailed report of a 27-year-old man with WHS [Opitz, 1995] and a 39-year-old man [Wheeler et al., 1995] provide insights into the morbidity associated with WHS in adulthood. Including our patient, in all three the congenital heart defect was not severe and consisted of mild ventricular septal defect. There was marked growth failure, contractures of hands, wrists, and feet, poor development of secondary sexual characteristics, and severe growth and intellectual handicap. Differences include lack of epilepsy in one case [Opitz, 1995], continuing epilepsy [Wheeler et al., 1995] and improvement in epilepsy from childhood to adulthood in our case.

Major structural anomalies of the brain have been described in one third of cases of WHS [Lazjuk et al., 1980]. Reported anomalies have varied from hypoplasia of the brain with narrow gyri to arhinencephaly and cysts in the subependymal region of the lateral ventricles. Hydrocephalus is a relatively common finding, as is skull asymmetry. In our patient, there was marked asymmetry of the cerebral hemispheres on CT scanning with the entire right hemisphere being smaller than the left. In addition, there was dilatation of the ventricles on the right, with small ventricles on the left and microgyria, consistent with the patient's left hemiplegia.

The extent of the deletion resulting in the WHS phenotype has been refined to the distal region of 4p16.3 by molecular techniques and FISH [Gandelman et al., 1992; Estabrooks et al., 1993]. The smallest DNA deletion involves 2.5 Mb. Whether the size of the deletion affects longevity is not known, but of the other two adults reported, one had a large deletion of ⅓ to ½ of 4p [Opitz, 1995] and the other resulted from an unbalanced translocation [Wheeler et al., 1995]. Further cases are required to clarify this aspect of the natural history of WHS, as longevity may be affected by imbalance of another small chromosomal segment. Our patient also has partial trisomy 4q. Congenital heart defect and epilepsy occur in cases of chromosome 4q+ [Angulo et al., 1984; Zollino et al., 1995]. The other pericentric inversion of chromosome 4 resulting in WHS, with breakpoints identical to our case and with partial trisomy 4q [Hirsch and Baldinger, 1993], also had congenital heart defect and epilepsy. The clinical findings in our patient were strongly suggestive of WHS and the karyotype was repeated with high resolution banding. In this family

the implications of precise diagnosis in the propositus has important reproductive implications for his sibs. The case illustrates the importance of reassessing patients with abnormal phenotypes previously reported as cytogenetically normal.

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